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Review Article

Importance of miRNAs in Cancer Therapy and Therapeutic Delivery Approaches

Esra Nur Gultekin[a,b] **Sevgi Marakli**[a*]

[a]Department of Molecular Biology and Genetics, Faculty of Arts and Sciences, Yildiz Technical University, Istanbul, Turkey
[b]Program of Molecular Biology and Genetics, Graduate School of Science and Engineering, Yildiz Technical University, Istanbul, Turkey

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ABSTRACT

Uncontrolled cell division and proliferation due to environmental and genetic factors are characteristics of cancer. Despite traditional treatments such as surgery, chemotherapy and radiation therapy, the incidence and mortality rate of cancer increases every year. Therefore, it is necessary to improve new treatment strategies such as microRNA (miRNA). miRNAs are non-coding endogenous RNA molecules with 18-22 nt in length. They regulate important pathways in different cancer types and play active roles in mechanisms such as proliferation, migration, apoptosis and invasion. Due to their functions in the pathogenesis of cancer as oncogenic or tumor suppressors, miRNAs have been currently used as therapeutic agents. However, the limited biological stability, inability to diffuse into the target tissue and their degradability by nucleases of miRNAs are disadvantages of miRNAs. Viral and non-viral miRNA delivery systems provide high transfection to target tissue and avoid nuclease-induced degradation. This study highlights the importance of miRNAs' regulatory involvement in cancer processes and therapeutic delivery approaches.

1. Introduction

Cancer is a complex disease resulting from genetic and environmental changes [1]. In 2020, cancer incidence was reported at 19.3 million and there were almost 10 million disease-related deaths [2]. It has been demonstrated that cancer is one of the reasons for mortality in both men and women between the ages of 60 and 79 [3]. Lung, stomach, liver, prostate, colorectal, cervical, thyroid and breast cancers are the most common types of cancer in humans. New diagnostic and therapeutic strategies have been improved to reduce the high incidence and mortality. In addition to traditional treatments (surgery, chemotherapy and radiation therapy), newly developed genomic diagnostic tools and treatment systems are used to destroy cancer cells or prevent their multiplication [1, 4-6].

miRNAs play important roles in cancer therapy resistance, progression, tissue differentiation, embryonic development, cell growth and apoptosis. Numerous studies have also revealed that miRNAs can be used as biomarkers for prognosis and diagnosis. Furthermore, innovative miRNA therapeutic systems provide the potentials for new therapeutic approaches to cancer treatment by modulating all biological pathways [7-9]. miRNAs are small non-coding RNA molecules with 18-22 nt in length. They regulate expression at post-transcriptional and post-translational levels [10]. The first miRNA, lin-4, was discovered in 1993. After the discovery of the first miRNA, 48,885 mature miRNAs were identified in 271 species. Today, miRNAs are known to be ubiquitously expressed in almost all cell types, regulating more than 30% of mammalian gene products [9, 11]. While a single miRNA binds to multiple targets, multiple miRNAs may be involved in the regulation of a single target [12-14].

The absence of a reliable delivery mechanism is one of the main barriers for the therapeutic application of miRNA. Therefore, researchers have worked to create new delivery methods, providing the highest level of miRNA efficacy while minimizing toxicities [15]. Viral and non-viral delivery systems are efficient methods for miRNA delivery. Viral delivery systems use adenovirus, retrovirus, lentivirus and adeno-associated viruses, whereas polymeric, organic and inorganic nanoparticles (NPs) are used in non-viral delivery systems [16, 17]. NPs have sizes between 1 and 100 nanometers. The size of NPs decreases, and surface area increases with high particle surface energy. Thus, NPs facilitate the access of miRNAs to the central nervous system (CNS) through the blood-brain barrier (BBB) and different biological barriers [18, 19]. NPs have been commonly used as anti-cancer agents with controlled drug release and tumor targeting [20]. The nanomedicine industry has been developing rapidly in recent years, and there are hundreds of nano-based products in preclinical and clinical development [21-23]. This review mentions the roles of miRNAs and therapeutic delivery strategies in cancer.

2. Using miRNAs as Cancer Therapeutics

miRNAs play crucial roles in gene expression regulation. These genes may be related to different pathways including homeostasis, growth and development, defense mechanisms and even apoptosis [24]. Cancer-associated miRNAs can be divided into two groups: oncogenic (oncomiRs) and tumor suppressor miRNAs. miRNAs in the first category are usually expressed at high levels and contribute to tumor progression. MiRNAs in the

*Corresponding author: Sevgi Marakli
*E-mail address: smarakli@yildiz.edu.tr
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second category are often downregulated in various cancers, and inhibit tumor formation by regulating cell growth, apoptosis and immune cell development [25].

2.1. Pancreatic Cancer

There are several reports to examine miRNAs in pancreatic cancer tissues. One of them was carried out by Meng et al. [26]. They showed a significant reduction in the expression of miR-146a-5p in pancreatic ductal adenocarcinoma (PDAC) when compared to adjacent tissues. Furthermore, they reported that when miR-146a-5p is introduced to PDAC cell lines, it binds to the 3′-UTR of TRAF6 and sensitizes PDAC cells to gemcitabine. It was also detected that miR-146a-5p regulates PDAC cell growth and chemoresistance by suppressing the TRAF6/NF-κB p65/P-gp axis.

IGF2 mRNA-binding protein 2 (IGF2BP2) is overexpressed in pancreatic cancer tissues, playing oncogenic roles. In this study, bioinformatic analyses showed that IGF2BP2 is a direct target of miR-141. Therapeutic delivery of miR-141 to cancer cells suppresses IGF2BP2 and induces apoptosis through PI3K/Akt signaling pathway [27]. Another study examines the activity of miR374a which promotes proliferation, migration and EMT in pancreatic cancer. Studies indicated that the inhibition of miR374a increases SRC Kinase Signaling Inhibitor 1 (SRCIN1) expression. SRCIN1 is characterized by low expression in pancreatic cancer, thereby inhibiting EMT and migration [28].

Seyed Salehi et al. [29] analyzed miRNA levels in the serum of 77 pancreatic cancer patients and 65 non-cancerous patients. According to the results of the study, they suggested that miR-125a-3p, miR-4530 and miR-92a-2-5p may be used as biomarkers for the diagnosis of non-invasive pancreatic cancer.

2.2. Lung Cancer

miR-196b-5p promotes cellular migration, proliferation ability and tumor growth in non-small cell lung cancer (NSCLC) by targeting the tumor suppressors GATA6 and TSPAN12. Furthermore, QKI-5 is a target of miR-196b-5p and shows low expression in NSCLC [30].

Jamal et al. [31] investigated miRNA-125a-5p which inhibits the expression of genes involved in epidermal growth factor receptor (EGFR) signaling pathway in lung cancer. They indicated that miRNA-125a-5p significantly increased the apoptotic effect of erlotinib which is an EGFR tyrosine kinase inhibitor and used as a therapeutic agent for NSCLC treatment.

High expression of cell death protein-1 ligand (PD-L1) reduces the survival rate in lung cancer [32]. The effects of miR-200 and miR-138 on PD-L1 were investigated by Zhang et al. [33]. Similarly, PTEN triggers cell death by suppressing PI3K/AKT signaling pathway. Inhibition of PTEN activates the PI3K/Akt pathway, causing tumor growth. It was determined that miR-425-5p, which is overexpressed in lung cancer, targets PTEN and triggers the PI3K/AKT pathway [34, 35].

2.3. Colon Cancer

miR-491-3p is a tumor suppressor miRNA and indicates low expression in colorectal cancers. On the other hand, increased expression of mitochondrial creatine kinase (uMtCK) in colorectal cancer is a characteristic of oncogenesis. Tang et al. [36] showed the suppression of uMtCK as a result of increasing expression of miR-491-3p.

PFKFB3 is a key enzyme responsible for controlling glycolysis. The increased expression of PFKFB was associated with tumor progression. However, the upregulation of miR-488 targeting PFKFB3 was found to inhibit tumor growth and increase chemotherapeutic efficacy in colorectal cancer patients [37].

Sphingosine-1-phosphate phosphatase 1 (SGPP1) plays a role in colorectal cancer and its overexpression is characterized by poor prognosis [38]. The regulation of SGPP1 via miR-656-3p is crucial for migration, invasion and cell proliferation in colorectal cancer [39]. Another important miRNA in colorectal cancer is miR-653-3p which targets SIRT1. The suppression of SIRT1 expression by miR-653-3p promotes genomic instability and inhibits apoptosis in colorectal cancer by activating the STAT3/TWIST1 pathway [40].

2.4. Breast Cancer

Telomeric repeat binding factor 2 (TRF2) is highly expressed in cancer and promotes tumor progression [41]. Therefore, it is important to reduce/suppress the expression of TRF2. Dinami et al. [42] studied the effect of miR-182-3p on TRF2, revealing the reduction of TRF2 expression because of increased expression of miR-182-3p.

In cancer cells, voltage-dependent anion channel 1 (VDAC1) interacts with Bcl-XL, Bcl-2 and HK proteins and provides escape from apoptosis. Normally, the expression of miR-874-3p targeting VDAC1 is low in cancer cells. It was reported that increased expression of miR-874-3p suppresses VDAC1 and induces apoptosis [43, 44].

Another example can be given for tumor protein D52 (TPD52). TPD52 is characterized by high expression in breast cancer. miR-1323 silencing increases TPD52 expression and leads to poor prognosis in breast cancer. Therefore, it is assumed that TPD52 and miR-1323 are thought to be potential therapies for breast cancer [45, 46]. On the other hand, the low expression of E-cadherin increases the capacity of cells to invade and metastasis [47]. Silencing the expression of miRNA-221-5p reduces metastasis via increasing e-cadherin in cancer cells [48].

2.5. Glioblastoma

miR-519a was less expressed in glioblastoma U87-MG/TMZ cells resistant to TMZ chemotherapeutic agent. As a result of increasing the expression of miR-519a, STAT3/BCL-2 signaling is inhibited, Beclin1 increases and induces autophagy [49]. Increased expression of miRNA-660-3p inhibits APOC1 and prevents migration and invasion. Another ncRNA, miRNA-660-3p, which directly targets APOC1, has low expression in GBM cells. Apolipoprotein C-1 (APOC1) leads to cell proliferation [50, 51].

The association of miRNAs with circRNAs has been confirmed in many studies. The expression level of miR-370-3p in GBM tissues is low when compared to normal tissues. Transforming growth factor beta receptor 2 (TGFBR2) triggers metastasis and invasion with high expression levels in these tissues. There is a close relationship among TGFBR2, miR-370-3p and circARID1A. miR-370-3p targets TGFBR2, whereas miR-370-3p is targeted by circARID1A. Therefore, circARID1A silencing also provides the binding of miR-370-3p to TGFBR2 and down-regulates it. Thus, migration and invasion are inhibited in GBM [52].

3. miRNA Delivery Strategies in Cancer Therapy

miRNAs can be used as therapeutic agents to reduce/prevent cancer pathogenesis due to their regulatory roles in cancer progression [16]. However, miRNAs cannot passively diffuse across lipid membranes into target cells and have very limited biological stability. Moreover, miRNA mimics or anti-miRNAs have challenges in their application such as avoiding nucleases and being delivered to the target site. These situations cause problems for delivery, and therefore producing effective delivery systems for in vitro and in vivo studies have gained interest. Viral and non-viral vectors have been developed for the delivery of miRNA mimics or anti-miRNAs for therapeutic purposes (Figure 1) [17, 53-55].

The pri-miRNA is transcribed into a mature miRNA in viral

delivery systems initiated by the viral promoter and cloned into the plasmid. Thus, it is provided to act on the target mRNA [56]. Adenovirus, lentivirus, retrovirus, herpesvirus, adeno-associated viruses and poxvirus are viral vector systems used for treatments [20, 57]. Although viral vectors have advantages of providing stable gene expression, they also have disadvantages such as lack of cell type specificity, the potential for carcinogenesis, immune response and the possibility of in vivo mutation [54, 58]. According to a study, 9 oncogenic miRNAs (miR-9-5p, miR-10b-5p, miR-21-5p, miR-23a-3p, miR-29a-3p, miR-155-5p, miR-222-3p, miR-301a-3p, and miR-373-3p) target the EMT pathway in breast cancer cells. By designing long non-coding RNA (lncRNA)(lncRNAi9) targeting the suppression of oncogenic miRNAs and transferring the viral vector AdSVP, target genes were regulated, and metastasis was reduced [59, 60]. According to another study in hepatocellular carcinoma, lncRNA was designed to simultaneously target miR-21, miR-153, miR-216a, miR-217, miR-494 and miR-10a-5p. The lncRNA was transferred to the viral vector to decrease the expression of target miRNAs to regulate sorafenib resistance [59, 61].

A non-viral delivery system prevents nuclease-mediated degradation during delivery of miRNA or miRNA-expressing vectors. Although transfection efficiency is low in these systems, they are generally less toxic and immune response is lower than viral vectors [15]. The low cost and versatility are other important advantages of non-viral delivery systems [53]. Lipid-based NPs, polymeric-based NPs, exosomes, metallic NPs, peptide NPs, etc. are examples of effective non-viral delivery systems for miRNA (Figure 1) [59, 62, 63].

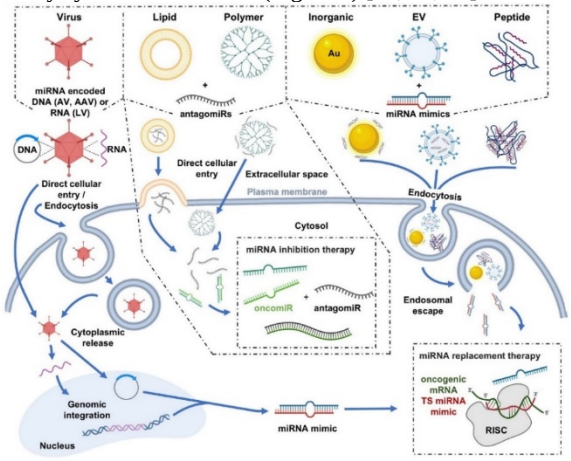

Fig. 1. Viral and non-viral miRNA delivery systems [59]

4. Nanoparticle-Mediated Delivery of miRNA

NPs have been utilized for numerous diseases, particularly cancer, and have gained attention in recent years [64]. Various imaging techniques such as electron microscopy (TEM, SEM), dynamic light scattering (DLS), photon correlation spectroscopy (PCS) and near-infrared spectroscopy have been commonly utilized for NPs' characterization [65]. miRNA-NPs combination can deliver to target tissues with high transfection [66]. Researchers believe that NPs are suitable delivery systems for miRNAs as therapeutic agents in various cancers [67]. The cancer and target genes of NP-mediated miRNAs were indicated in Table 1.

5. Conclusion

Cancer is one of the most important diseases, resulting in approximately 18 million new cases and 9,6 million deaths in a year [89]. Different genes belonging to several pathways play crucial roles in cancer pathogenesis, and miRNAs are important regulators in the expression of these genes [90-93]. However, the effects of miRNAs on cancer genetics are still unclear since the mechanism behind their tumor suppressor and oncomiR properties is still unknown [16]. For example, miR-10b is an oncogenic ncRNA with high expression in GBM, causing a poor prognosis in cancer. In contrast, miR-10b is a tumor suppressor in cervical cancer and gastric cancer [15, 94, 95]. In addition, miRNAs have low stability and limited cellular transduction, reducing their therapeutic effect in cancer [96]. These drawbacks have led researchers to improve NP-based systems as a more effective delivery form in the treatment of cancer metastasis and chemoresistance [97]. Especially in recent years, NPs have been frequently used in several investigations [53, 67, 98]. Furthermore, the therapeutic effect of miRNAs can be enhanced by combination with chemotherapeutic drugs [54]. For example, delivery of anti-miR-221 therapy with TMZ and silica-based NP has been found to enhance the therapeutic effect in glioma cancer [99].

In conclusion, the oncogenic and tumor suppressor properties of miRNAs have made them effective therapeutic agents in cancer. The most effective method of delivering miRNAs in clinical settings is thought to involve optimizing various approaches. Furthermore, it is believed that the understanding of the molecular mechanism underlying miRNAs' effects on cancer will be beneficial for cancer treatments in the future.

Table 1. Nanoparticle-delivered miRNAs, cancer and target genes

Nanoparticles (NPs)	miRNA	Cancer	Target gene	Reference
Polymeric NPs	miR-103a	Globlastoma	FGF2–XRCC3	[68]
Lipid NPs	miR-634	Pancreatic cancer	APIP, XIAP, BIRC5, TFAM, LAMP2	[69]
Exosome NPs	miR-199a-3p	Ovarian cancer	Met, mTOR , IKKβ	[70]
Lipid NPs	miR-143/145	Pancreatic cancer	KRAS2,IFN-y, RREB1	[71]
Polymeric NPs	MiR-34a	Colon cancer	Bcl-2	[72]
Polymeric NPs	miR-122	Hepatocellular Carcinoma	ADAM17	[73]
Polymeric NPs	miR-143	Prostate cancer	UPAR	[74]
Lipid NPs	miR-21	Lung cancer	-	[75]
Lipid NPs	miR-146a	Myloid cancer	IRAK1, TRAF6	[76]
Metallic NPs	miR-206	Breast cancer	NOTCH3	[77]
Magnetic NPs	miR-7-5p	Colorectal cancer	KLF4	[78]
Polymer-peptide NPs	miR-559	Breast cancer	HER-2	[79]
Lipid NPs	miR-214	Intestinal cancer	p53	[80]
Polymeric NPs	miR-200c-3p	Breast cancer	ZEB1, ZEB2	[81]
Polymeric NPs	miRNA-21	Glioblastoma	PTEN	[82]
Peptide NPs	miR-9	Pancreatic cancer	eIF5A2	[83]
Lipid-Exosome NPs	miR-497	Ovarian cancer	PI3K/AKT/mTOR	[84]
Metallic NPs	miR-21–3p	Melanoma	PD-1, IFN-y	[85]
Lipid NPs	miR-34a	Head and neck cancer	-	[86]
Lipo-polymeric NPs	miR-34a	Breast cancer	Bcl-2, Ki-67, Bax	[87]
Polymeric NPs	miR-22	Osteosarcoma	PI3K/AKT	[88]

Declaration of conflicting interests

The authors declare no competing interests.

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